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ASBMT EXPERT PANEL REPORT

The Role of Cytotoxic Therapy With Hematopoietic Stem Cell Transplantation in the Therapy of Diffuse Large Cell B-Cell Non-Hodgkin's Lymphoma: An Evidence-Based Review

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**All abbreviations are defined at first reference in the text and in Appendix A.*

I. INTRODUCTION

The American Society for Blood and Marrow Transplantation (ASBMT) in 1999 began an initiative to sponsor evidence-based reviews of the scientific literature for the use of blood and marrow transplantation in the therapy of selected diseases. A steering committee was convened to oversee the project and to appoint an independent panel of experts to conduct each review.

The following is the first review to result from the initiative. Its goals were to:

1. assemble and critically evaluate all of the evidence regarding the role of cytotoxic therapy with hematopoietic stem cell transplantation (SCT) in the therapy of diffuse large cell B-cell non-Hodgkin's lymphoma (DLCL);
2. make treatment recommendations based on the available evidence; and
3. identify needed areas of research.

The published literature was graded on the quality of design (Table 1) and the strength of the evidence (Table 2) in a systematic manner. Treatment recommendations were subsequently graded based on the quality and strength of the evidence (Table 3). The treatment recommendations of the expert panel based on these criteria for evaluating the evidence are detailed in Section X (Tables 13 and 14).

At least one prospective multicenter (international) randomized clinical trial is represented in each of the major sections of this review, including:

- comparison of SCT to standard chemotherapy in first or subsequent relapse;
- first complete response/remission (CR) after full-course standard induction;
- first partial response/remission (PR) after abbreviated standard induction; and
- up-front high-dose sequential therapy.

Other supporting evidence is described, as well as studies that investigate special subgroups (eg, age, immunophenotype) and specific SCT techniques (eg, tandem/double transplantations, stem cell mobilization, autologous versus allogeneic SCT).

II. LITERATURE SEARCH METHODOLOGY

MEDLINE, the Web site of the National Library of Medicine, National Institutes of Health, was searched using the MeSH term "Non-Hodgkin's Lymphoma" limited to "Drug Therapy" or "Therapy." Search criteria were limited to English language, human trials, and publication dates between January 1980 and December 2000. In addition, a hand search was conducted of abstracts published by the American Society of Hematology in *Blood*, the American Society of Clinical Oncology in *Journal of Clinical Oncology*, and the European Group for Blood and Marrow Transplantation in *Bone Marrow Transplantation* for the meeting years 1997-2000; and for abstracts published in *Annals of Oncology* by the International Conference on Malignant Lymphoma for the 1999 meeting year.

DLCL was defined as the Revised European-American Classification of Lymphoid Neoplasms (REAL) [1] or World Health Organization (WHO) [2] classification of diffuse large B-cell lymphoma; or International Working Formulation (IWF) [3] subtypes F (diffuse mixed large and small cells), G (diffuse large cell) and H (diffuse large cell immunoblastic); or Kiel Classification [4,5] centroblastic, centroblastic-centrocytic (diffuse), centrocytic (large) and immunoblastic B-cell; or Rappaport classification [6] diffuse histiocytic B-cell lymphoma.

Published articles and abstracts studying SCT were included only if DLCL patients made up a minimum of 70% of the study population, unless results were stratified by histology subtype. The proportion of the study population with anaplastic large cell lymphoma is presented in the grading summary at the end of each major section but was not considered in calculating the 70% minimum required for inclusion.

More than 250 abstracts and manuscripts that met the initial search criteria were ultimately excluded because they:

- did not study cytotoxic therapy with SCT;
- studied therapy for relapse after SCT (studies of second transplantations were not excluded);
- did not assess overall survival (OS), disease-free survival (DFS) or event-free survival (EFS) (with the exception of studies of stem cell mobilization techniques);
- did not state the histologic subtypes (by IWF, Kiel, Rappaport, REAL or WHO classifications);
- stated the histologic subtypes but included fewer than 70% DLCL patients or did not stratify the results by subtype;
- studied HIV-associated lymphomas;
- conducted a Phase I study (dose-escalation or dose-finding study);
- were reviews of the literature, editorials, case reports, or letters to the editor; and/or
- were abstracts subsequently published as manuscripts.

A list of all excluded manuscripts and abstracts is available at the ASBMT Web site www.asbmt.org.

III. QUALITATIVE AND QUANTITATIVE GRADING OF EVIDENCE

The hierarchy of evidence, including a grading scheme for the quality of the evidence, strength of the evidence, and strength of each recommendation, has been established and published as an editorial policy statement in *Biology of Blood and Marrow Transplantation* [7]. Tables 1 to 3 are reprinted from the policy statement and define the criteria used to grade the studies included in the review and the treatment recommendations. Study design, including sample size, patient selection criteria, duration of follow-up, and treatment plan, also were considered in evaluating the studies.

IV. FIRST OR SUBSEQUENT RELAPSE

There has been only 1 randomized multicenter trial (level 1 evidence; Table 1) comparing autologous bone marrow transplantation (BMT) with standard salvage chemotherapy in relapsed DLCL patients. This trial is described in detail in the chemotherapy-sensitive relapse section below, along with supporting evidence from retrospective cohort and prospective phase II studies (level 2 evidence; Table 1).

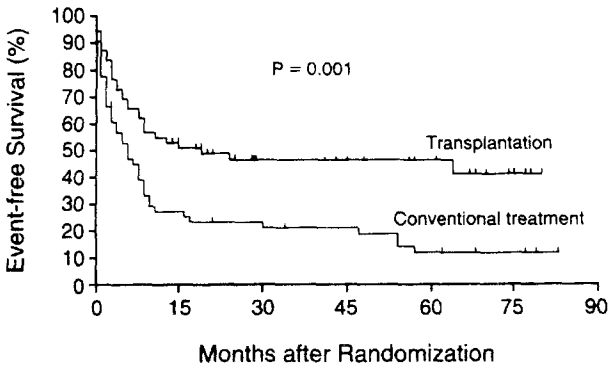

Figure 1. Kaplan-Meier curves for event-free survival of patients in the transplantation and the conventional treatment groups. The data are based on an intention-to-treat analysis. Tick marks represent censored data. Reprinted with permission from Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med.* 1995;333:1540-1545. Copyright © 1995 Massachusetts Medical Society. All rights reserved.

There have been no randomized trials that include DLCL patients with chemotherapy-resistant, primary refractory, or untested relapsed disease. The results of several retrospective cohorts and prospective phase II efficacy studies that compare the impact of chemotherapy sensitivity to the impact of chemotherapy resistance on BMT outcome are summarized in the following appropriate sections.

A. Chemotherapy-Sensitive Disease

The PARMA trial compared autologous BMT with salvage chemotherapy in chemotherapy-sensitive non-Hodgkin's lymphoma (NHL) patients [8-10]. A total of 215 intermediate- or high-grade NHL patients in first (n = 188) or second (n = 27) relapse were enrolled. To be eligible, patients must have received a doxorubicin-containing induction regimen and maintained a CR for a minimum of 4 weeks. All patients received 2 salvage courses of dexamethasone, cisplatin, and cytarabine (DHAP). Bone marrow (BM) was harvested after the first course of DHAP.

One hundred nine patients with CR or PR to DHAP were randomized to receive 4 additional DHAP courses and involved field radiotherapy (IFRT) to bulky disease sites (n = 54) or autologous BMT with carmustine, etoposide, cytarabine and cyclophosphamide (BEAC) conditioning and IFRT to bulky disease sites or extranodal lesions (n = 55). Prognostic factors were similar in the 2 groups.

With a median follow-up of 63 months, the overall response rate was 84% after BMT versus 44% after salvage chemotherapy. The 5-year EFS was 46% in the BMT group versus 12% in the chemotherapy group (P = .001). OS at 5 years was 53% in the BMT group versus 32% in the conventional treatment group (P = .038 [Figure 1]).

A subsequent retrospective analysis of the PARMA trial [11] investigated the prognostic value of the International Prognostic Index (IPI) at relapse [12]. (See Appendix B for definitions of the IPI risk categories.) At a 79-month median follow-up, the 5-year OS was 46%, 25%, 25% and 11% for patients with an IPI of 0, 1, 2, and 3, respectively (P < .001). As shown in Figure 2, IPI at relapse was significantly correlated with OS in the salvage chemotherapy group (5-year OS 48%, 21%, 33%, 0% for IPI 0, 1, 2, 3, respectively [P = .006]) but not in the BMT group (5-year OS 51%, 47%, 50%, 50% for IPI 0, 1, 2, 3, respectively [P = .90]). OS was

Table 1. *Grading the Quality of the Evidence**

I	**Evidence obtained from at least one properly randomized controlled trial**
II-1	**Evidence obtained from well-designated, controlled trials without randomization**
II-2	**Evidence obtained from well-designated, cohort or case-controlled analytic studies, preferably from more than one center or research group**
II-3	**Evidence obtained from multiple timed series with or without the intervention, or from dramatic results in uncontrolled experiments**
III	**Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees**
IV	**Evidence inadequate owing to problems of methodology, e.g., sample size, length or comprehensiveness of follow-up, or conflict in evidence**

*Reprinted with permission from Shipp MA, Abeloff MD, Antman KH, et al. International Consensus Conference on High-Dose Therapy with Hematopoietic Stem Cell Transplantation in Aggressive Non-Hodgkin's Lymphomas: report of the jury. *J Clin Oncol.* 1999;17:423-429.

Table 2. *Grading the Strength of the Evidence**

1	**Experimental therapy significantly better (P < 0.05)**
2	**Trend in favor of experimental therapy (P > 0.05)**
3	**No apparent statistical effect**
4	**Trend favoring control group (P > 0.05)**
5	**Control group significantly better (P < 0.05)**

*Reprinted with permission from Chalmers TC, Berrier J, Sacks HS, Levin H, Reitman D, Nagalingam R. Meta-analysis of clinical trials as a scientific discipline. II: Replicate variability and comparison of studies that agree and disagree. *Stat Med.* 1987;6:733-744.

Table 3. *Grading the Strength of the Treatment Recommendation**

A	**Effective treatment**
B	**Marginally effective treatment**
C	**Not an effective treatment (no statistical or clinical difference between therapies)**
D	**Inadequately evaluated treatment and recommended for comparative study**
E	**Inadequately evaluated treatment but not recommended for comparative study**

*Based on Tables 1 and 2. Reprinted with permission from Jones R, Horowitz M, Wall D, et al. ASBMT policy statement regarding the methodology of evidence-based reviews in evaluating the role of blood and marrow transplantation in the treatment of selected disease. *Biol Blood Marrow Transplant.* 2000;6:524-525.

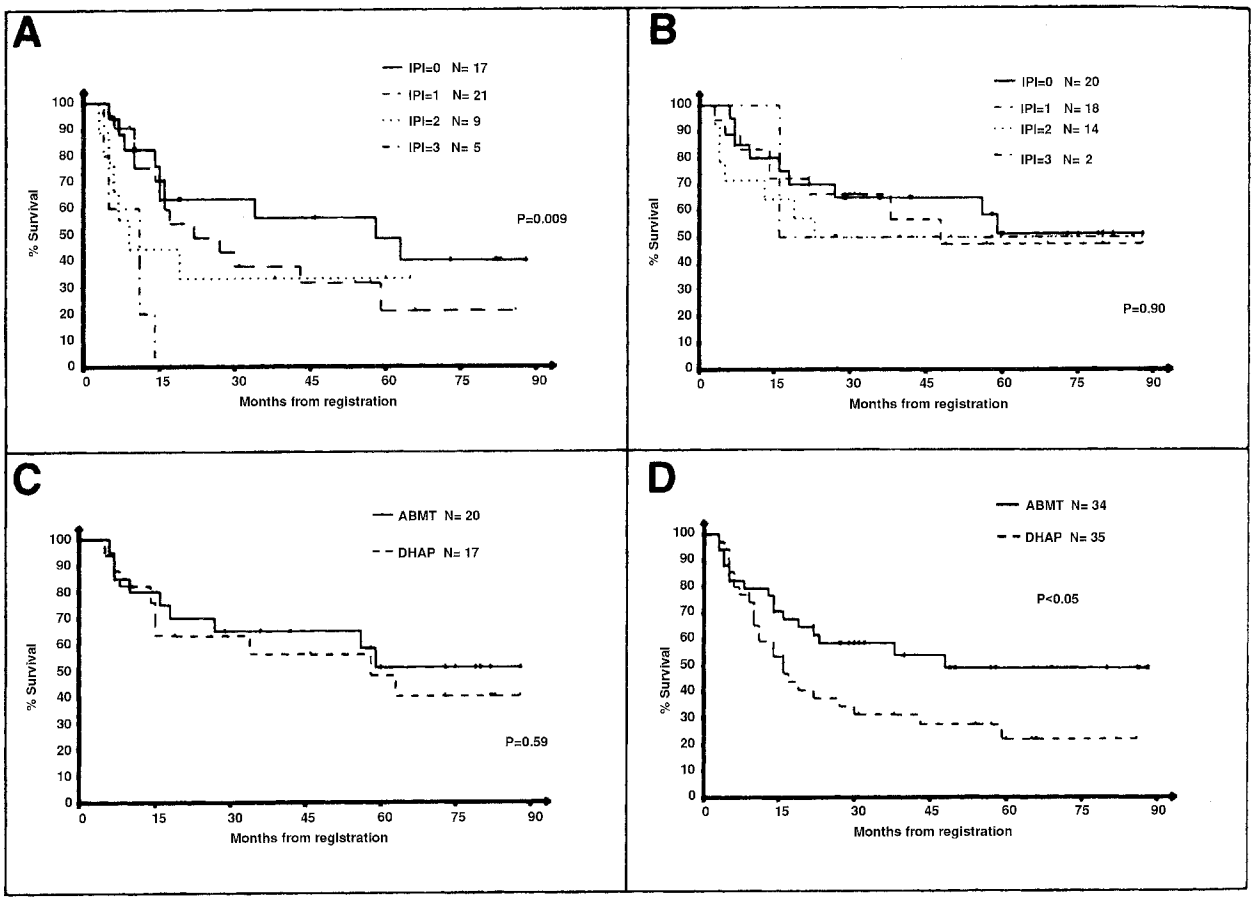

Figure 2. Overall survival of 106 randomized patients according to the International Prognostic Index (IPI) at relapse. Survival is calculated from the first day of the first course of dexamethasone, cisplatin, and cytarabine (DHAP). A, Survival of patients in the DHAP arm according to the IPI. B, Survival of patients in the ABMT arm according to the IPI. C, Patients with IPI = 0, DHAP versus ABMT arm. D, Patients with IPI = 1-3, DHAP versus ABMT arm. Reprinted with permission from Blay JY, Gomez F, Sebban C, et al. on behalf of the PARMA Group. The International Prognostic Index correlates to survival in patients with aggressive lymphoma in relapse: analysis of the PARMA trial. *Blood.* 1998;92(10):3562-3568. Copyright ©1998 American Society of Hematology.

significantly better in the BMT group compared to the salvage chemotherapy group in patients with an IPI >0, but not in the patients with an IPI = 0.

The PARMA trial's results were assessed by Kanjeekal et al. in a population of patients who did not meet the trial's strict eligibility criteria [13]. (This study did not give information on histology; however, patient selection was based on factors comparable to those in the PARMA trial, in which 73% of patients were diagnosed with DLCL.) Two reviewers blinded to treatment and outcome retrospectively reviewed 60 patients, 27 of whom received SCT. Among those who received SCT, 19% (5/27) were "PARMA eligible." Eighty-one percent (22/27) did not meet the eligibility criteria of the PARMA trial due to primary refractory disease (26%), failure to achieve a PR (20%), salvage therapy other than DHAP (48%), or age greater than 60 years (30%). There was no detectable difference in the 2-year progression-free survival (PFS) (P = .38) or OS (P = .41) between PARMA eligible and ineligible patients.

Among the 27 SCT patients, 17 (63%) were judged appropriate for SCT using the PARMA eligibility criteria; 10 (37%) were judged inappropriate. There was no significant difference in the 2-year PFS (32% versus 15%; P = .3) or OS (48% versus 30%; P = .14) between the groups judged appropriate and inappropriate for SCT using the PARMA eligibility criteria.

Prince et al. sought to retrospectively identify major prognostic factors predicting outcome in 81 patients with chemotherapy-sensitive relapsed disease (at minimum, a PR to salvage therapy after first relapse) who underwent transplantations with melphalan and etoposide with or without total body irradiation (TBI) [14]. Their multivariate model assessed the following variables: age, histology, stage at diagnosis, immunophenotype, extranodal disease at diagnosis, prior BM involvement, bulky disease at diagnosis, duration of prior CR, number of cycles of conventional-dose salvage chemotherapy, tumor burden at relapse, relapse in a previous radiation field, and remission status immediately prior to BMT. Remission status at BMT was the only significant variable that predicted OS and PFS (P = .0001). Patients who received transplants in CR had a significantly better 4-year OS and PFS than those who received transplants in PR (OS 72% versus 26%; PFS 61% versus 25%).

Verdonck et al. used an alternative salvage regimen of prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, mechlorethamine, vincristine, and procarbazine (ProMACE-MOPP) before BMT in 31 patients with primary refractory disease or relapsed from CR after induction with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) [15]. Of 28 ProMACE-MOPP responders, 17 (61%) patients underwent autologous BMT with cyclophosphamide and TBI (CT) conditioning. Of the 31 ProMACE-MOPP patients, there was an overall response (CR/PR) rate of 90% with a 3-year DFS of 25%.

Stamatoullas et al. studied the feasibility of peripheral blood SCT (PBSCT) for patients over the age of 60 [16]. Of the 13 enrolled in the study, 9 patients, with a median age of 62 (range, 61-70), underwent PBSCT with carmustine, etoposide, cytarabine, and melphalan (BEAM) conditioning regimen; at transplantation, 8 had chemotherapy-sensitive disease (first or second CR) and 1 had primary refractory disease. Of the 8 with chemotherapy-sensitive disease at transplantation, there was 1 early toxic death, 4 patients relapsed and died during the first 3 months post-PBSCT, and 3 are alive in CR 8 to 14 months post-PBSCT. Before PBSCT, all patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) <2. At discharge, 7 of the 8 surviving patients had an ECOG PS of 3, and only 2 recovered to a PS of 0 at 2 and 5 months post-PBSCT. The remaining 5 relapsed before PS recovery.

Guglielmi et al. retrospectively analyzed 247 DLCL patients who underwent transplantation in first chemotherapy-sensitive relapse to determine which factors were predictive for OS and EFS [17]. Sixty-two percent of the patients had a low- or low-intermediate–risk IPI score at time of diagnosis. First relapse occurred a median of 258 days after first CR, and SCT was performed a median of 153 days after first relapse. OS was 52% and EFS was 45% at 5 years. Three factors had independent prognostic value by multivariate analysis: BM involvement at first relapse, PS at first relapse, and duration of first CR. The effects of the 3 factors were cumulative: 30% had no adverse factors with an OS of 76% and EFS of 69%; 51% had 1 adverse factor with an OS of 55% and EFS of 48%; 19% had 2 or 3 adverse factors with an OS of 31% and EFS of 21%.

The Evidence for Transplantation in Chemotherapy-Sensitive Relapsed Disease

There are no prospective studies comparing conditioning regimens, stem cell mobilization techniques, stem cell source, or donor type for chemotherapy-sensitive relapsed disease. The only evidence that has been systematically evaluated is the PARMA trial [8-10] using BEAC conditioning and autologous BM as a stem cell source. Although there is no evidence specific to DLCL patients, the standard of care has changed from using autologous BMT to autologous PBSCT. This change is based on registry data, retrospective comparisons, and clinical experience, including all NHL subtypes. (PBSCTs have not been rigorously compared to BMTs in prospective clinical trials in DLCL patients; however, PBSCTs appear to result in improved outcomes in a variety of diseases.)

There are no data to establish whether allogeneic donors, immunotherapy, or conditioning and stem cell mobilization regimens different than those used in the PARMA trial may improve outcomes in chemotherapy-sensitive relapsed DLCL patients. These are possible areas for future research.

The following 2 sections summarize feasibility studies of purging and immunotherapy in chemotherapy-sensitive relapsed DLCL patients.

Purging or Positive Selection. Weisdorf et al. performed a prospective nonrandomized trial using in vitro–purged autologous BMT in 70 patients with low-grade (n = 15), intermediate-grade (n = 25) or high-grade (n = 30) NHL (results stratified by NHL grade) [18]. Marrow obtained from 42 patients with B-cell immunophenotype was purged in vitro with monoclonal antibodies (anti-CD9, -CD10, and -CD24) plus complement. Twelve patients with T-cell immunophenotype received marrow purged with monoclonal antibodies conjugated with immunotoxins (anti-CD5– and anti-CD7–ricin conjugates) and 4-hydroperoxycyclophosphamide; 16 patients received unpurged BM. Seventy percent of patients had either chemotherapy-sensitive or untested relapsed disease or a PR to induction therapy at time of transplantation; the remainder had primary refractory or chemotherapy-resistant relapsed disease.

The data on purging technique and patient characteristics summarized above are for all 70 NHL patients. Among intermediate-grade (92% IWF F/G) NHL patients (n = 25), there was no difference in hematologic recovery between purged and unpurged BMTs. At day 28 post-BMT, 69% were alive in CR. The 2-year OS and EFS were 31% and 24%, respectively. Purging technique (T versus B versus no purging) and immunophenotype (T versus B) had no association with relapse or survival post-BMT.

Use of Immunotherapy. Weinberger et al. performed a feasibility study using anti-CD20 antibody (rituximab) treatment before PBSC collection and after PBSCT in 5 patients either with chemotherapy-sensitive relapsed disease (n = 3) or with disease refractory to induction but sensitive to salvage therapy (n = 2) [19]. Rituximab was administered twice over 2 weeks prior to hematopoietic growth factor–mobilized PBSC collection, followed by PBSCT. Cyclophosphamide, carmustine, and etoposide (CBV) or etoposide and cyclophosphamide plus TBI (VCT) were used as conditioning. After hematologic recovery and before day 42 post-PBSCT, 2 additional weekly doses of rituximab were administered. The addition of rituximab to the pre- and posttransplantation regimen was well tolerated without evidence of delayed engraftment. All 5 patients remained in remission 37 to 355 days post-PBSCT.

Table 4 summarizes the evidence outlined above from the published literature studying SCT in chemotherapy-sensitive relapsed disease.

B. Chemotherapy-Resistant Relapse and Primary Refractory Disease

Two early studies demonstrated the feasibility of BMT as salvage therapy in poor-prognosis patients for chemotherapy-resistant relapse or primary refractory disease [20,21]. Subsequent studies have compared the efficacy of BMT in NHL patients by remission status at time of BMT. All studies have shown that patients undergoing

Table 4. *Grading Summary of the Evidence for SCT in Chemotherapy-Sensitive Relapsed Disease**

Reference	Quality of Evidence†	Strength of Evidence†			Median Follow-up, mo	No. of Patients	ALCL	IWF F/G/H
		OS	EFS	DFS				
Philip et al. [8]	I	I	I	NA	63	109	0%	73%
Blay et al. [11]	I	I‡	NA	I‡	79	215	0%	73%
Kanjeekal et al. [13]	2-2	3	NC	3	NS	27	§	§
Prince et al. [14]	2-1	NC	NA	NC	37	81	0%	80%
Verdonck et al. [15]	2-1	NA	NA	NC	33	17	0%	71%
Stamatoullas et al. [16]	2-1	NC	NC	NC	NS	13	0%	92%
Guglielmi et al. [17]	2-2	NC	NC	NC	48	247	NS	100%
Weisdorf et al. [18]	2-1	NC	NA	NC	36	70	0%	F/G 92% H 30%
Weinberger et al [19]	2-1	NA	NA	NA	NS	5	0%	100%

*SCT indicates hematopoietic stem cell transplantation; OS, overall survival; EFS, event-free survival; DFS, disease-free survival; ALCL, anaplastic large cell lymphoma; IWF, International Working Formulation; F, diffuse mixed cell; G, diffuse large cell; H, diffuse large cell immunoblastic; NC, no comparison in study between HDT/SCT and standard chemo; NA, not applicable; NS, not stated.

†See Tables 1 and 2 for definitions.

‡For patients with an IPI >0.

§Histology not stated; however, study eligibility criteria same as that for Philip et al. [8].

BMT for chemotherapy-resistant relapsed and/or primary refractory disease have significantly decreased survival compared to patients who received transplants for chemotherapy-sensitive disease [22-31]. Two studies showed the same effect in patients with primary mediastinal DLCL [32,33]. One study also demonstrated that DLCL patients with relapsed or refractory primary mediastinal disease had improved DFS and OS compared to DLCL patients with disease at other sites [33]. Although these studies are level 2 evidence (Table 1), the data are consistent across multiple centers. Tables 5 and 6 summarize the range of OS, or EFS and DFS, or PFS by chemotherapy sensitivity for these studies.

Kewalramani et al. retrospectively analyzed outcomes for 85 primary refractory NHL patients [34]. Forty patients had a PR after induction therapy (IPR) and 45 patients experienced induction failure (IF). Patients were given 3 cycles of ifosfamide, carboplatin, etoposide/granulocyte colony–stimulating factor (ICE/G-CSF) to mobilize PBSCs that were collected after the third cycle. Conditioning regimens were CBV, BEAM, high-dose ICE, ifosfamide/etoposide/TBI, or VCT, depending on age, prior therapy, and active trials at time of SCT.

Of 85 patients who underwent ICE/G-CSF chemotherapy and mobilization, 43 (50.6 %) achieved a CR (n = 14) or PR (n = 29). Five of these 43 patients had progressive disease before conditioning regimen and did not receive transplants. In addition, 4 patients who failed to respond to ICE underwent SCT. Among the 42 PBSCT patients, 4 died of progressive disease before day 100, none of transplantation-related causes. OS was 52.5% and EFS was 44.2%. In an intent-to-treat analysis, the 3-year OS and EFS were 25% and 22%. The IPR group had a statistically significantly higher OS compared to the IF group (P = .015). There was no significant difference, however, in EFS between the groups (P = .081). For the subset of patients who underwent autologous SCT, there was no difference in the OS or EFS between the IPR and IF groups.

The Evidence for Transplantation in Chemotherapy-Resistant/Refractory Disease

There are no prospective randomized trials comparing stem cell source, donor type, conditioning, or mobilization regimens in chemotherapy-resistant relapsed or primary refractory DLCL patients. The following sections summarize the level-2 evidence concerning IFRT, stem cell sources, stem cell mobilization regimens, allogeneic BMTs, and immunotherapy in resistant/refractory patients.

Role of Involved Field Radiotherapy. Mundt et al. evaluated the role of IFRT on the rate and sites of relapse in DLCL patients [35]. Fifty-three adult patients with refractory (n = 14) or relapsed (n = 39) disease underwent BMT or PBSCT with chemotherapy-only conditioning regimens. Seven (13%) patients received IFRT before (n = 1) or after (n = 6) SCT. Among patients surviving beyond day 30 post-BMT, none of the 7 IFRT patients relapsed in prior sites of disease, compared to 16 of 39 (41%) patients without IFRT. Three of 7 (43%) patients with IFRT and 12 of 39 (31%) patients without IFRT relapsed in new sites of disease. There were 141 sites of disease before induction therapy. The most common site was nodal (79%), 12% of which were ≥5 cm. Patients who received IFRT had significantly improved 4-year local control overall compared to those who did not receive IFRT (100% versus 61.1%; P = .05), in sites failing to achieve CR to induction (100% versus 32%; P = .01) and in sites failing to achieve a CR to SCT (100% versus 29.4%; P = .01).

Hematopoietic Stem Cell Sources. Vose et al. performed a retrospective multivariate analysis of 158 relapsed or primary refractory DLCL patients in order to develop a prognostic model for autotransplantation patients [36]. Good prognosis was defined as no mass ≥10 cm and no more than 1 of the following adverse factors: 3 or more prior chemotherapy regimens, serum lactate dehydrogenase (LDH) level greater than normal, chemotherapy resistance. The poor-prognosis group included patients with a mass ≥10 cm or with 2 adverse factors.

In the poor-prognosis group, there was no difference in the 3-year EFS in patients who received autologous BM

Table 5. *Comparison of Overall or Event-Free Survival by Disease Status at Time of SCT**

Reference	Number of Patients	Overall or Event-Free Survival					Kaplan-Meier Survival Percentages		
		2 y	3 y	4 y	5 y	6 y	Resistant Relapse/Refractory	Chemo-sensitive Relapse	Untested Relapse
Gribben et al. [27]	50	OS					1/30†	12/20†	
Stiff et al. [24]	94		OS				29%	55%	
Saez et al. [22]	45		OS				8%	63%	25%
Wheeler et al. [26]	78		EFS‡				22%	54%	
Popat et al. [33]	59DLCL 31PML			OS			32%	50%	
Mills et al. [23]	107				EFS		10%	56%	
Caballero et al. [30]	366					OS	4%	CR1 71% CR2 55% SD 46%	

*SCT indicates hematopoietic stem cell transplantation; OS, overall survival; EFS, event-free survival; DLCL, diffuse large cell B-cell non-Hodgkin's lymphoma; PML, primary mediastinal DLCL; CR, complete remission; SD, sensitive disease.

†Raw data were presented for individual patients; Kaplan-Meier survival percentages were not stated in the article.

‡Median survival times: 4.512 y for chemo-sensitive relapsed patients; 0.178 for chemo-resistant relapsed/refractory patients ($P < .001$).

compared with those who received PBSCs (10% versus 12%). In the good-prognosis group, patients who received autologous PBSCs had an improved 3-year EFS compared with those who received autologous BM (70% versus 32%; $P < .008$).

Stem Cell Mobilization. A variety of mobilization regimens have been used for several disease indications. Following are data on 3 regimens that have been analyzed specifically in DLCL patients.

Petit et al. treated 14 resistant/relapsed NHL patients (12 DLCL) with etoposide, methylprednisolone, high-dose cytarabine, and cisplatin (ESHAP) and G-CSF for PBSC mobilization [37]. This feasibility study demonstrated that this regimen could effectively mobilize PBSCs with few (1-2) aphereses and low toxicity in most patients.

Donato et al. treated 36 relapsed/primary refractory NHL patients with high-dose ifosfamide, etoposide, and G-CSF for PBSC mobilization with minimal toxicity [38]. A median of 2 collections yielded $CD34^+$ cells of greater than 4×10^6/kg. Median time to neutrophil engraftment after PBSCT was rapid for 15 patients receiving their first transplant (10 days) and 16 patients receiving their second transplant (9 days).

Haioun et al. demonstrated that the addition of stem cell factor (SCF) to cyclophosphamide/G-CSF mobilization increased the number of patients who achieved a sufficient

Table 6. *Comparison of Disease-Free or Progression-Free Survival by Disease Status at Time of SCT**

Reference	Number of Patients	Disease-Free or Progression-Free Survival					Kaplan-Meier Survival Percentages		
		2 y	3 y	4 y	5 y	6 y	Resistant Relapse/Refractory	Chemo-sensitive Relapse	Untested Relapse
Gribben et al. [27]	50	DFS					0/3†	6/11†	
Stiff et al. [24]	94		PFS				22%	42%	
Santini et al. [25]	54		PFS				11%	53%	
Philip et al. [29]	100		DFS				RR-14% Ref-0%	36%	
Saez et al. [22]	45		DFS				8%	56%	13%
Gulati et al. [28]	35		DFS				13%	CR-70% PR-62%	
Wheeler et al. [26]	78			FFP				58%	
Popat et al. [33]	59DLCL 31PML			DFS			32%	50%	
Mills et al. [23]	107				PFS		13%	49%	>49%
Sehn et al. [32]	35PML				PFS		33%	75%	
Caballero et al. [30]	366					PFS	38%	CR1-76% CR2-50% SD-38%	

*SCT indicates hematopoietic stem cell transplantation; DFS, disease-free survival; PFS, progression-free survival; RR, resistant relapse; Ref, refractory; CR, complete remission; PR, partial remission; FFP, freedom from progression; DLCL, diffuse large cell B-cell non-Hodgkin's lymphoma; PML, primary mediastinal DLCL; SD, sensitive disease.

†Raw data were presented for individual patients; Kaplan-Meier survival percentages were not stated.

$CD34^+$ cell yield (12×10^6 CD34/kg) with a reduced number of aphereses to support high-dose therapy with SCT [39].

HLA-Matched Sibling Allogeneic Transplantations. A retrospective analysis of outcomes and prognostic factors in 64 patients who underwent matched sibling-donor transplantations was conducted by van Besien et al. [40]. Among these patients, 14 were intermediate-grade NHL (93% DLCL), the majority of whom (n = 13) had refractory disease or more than 1 relapse (median number of prior regimens, 3). All intermediate-grade patients were treated with cyclosporine for graft-versus-host disease (GVHD) prophylaxis; 5 of 14 had TBI-containing conditioning regimens, and 71% had a Karnofsky Performance Status (KPS) ≥80. Half of the intermediate-grade NHL patients died of regimen-related toxicity (7/14), 4 patients died of progressive disease, 1 of infection, and 1 of GVHD. With a median follow-up of 38 months, the 2-year OS and DFS were 21% and 0% for this population of DLCL patients.

Autologous GVHD. In an attempt to lower the relapse rate after autologous BMT, Gryn et al. treated 40 refractory/relapsed DLCL patients with cyclosporine and interferon after autologous BMT to induce autologous GVHD [41]. Fifty-three percent of the patients developed grade I GVHD (erythroderma) at a median of 20 days following BMT; the GVHD lasted a median of 10 days and resolved without treatment in all cases. After a median follow-up of 24 months, 10% died of regimen-related toxicities, 13% relapsed, and the 2-year DFS was 77%. No patients developed chronic renal insufficiency and none died of renal complications. Multivariate analysis could not identify any significant predictors of relapse.

The evidence for SCT in these patient populations is summarized in Table 7.

C. Untested Relapse

The data regarding transplantation for patients with untested relapsed disease are not consistent and probably reflect differences in patient selection criteria among treatment centers. One study found that patients undergoing transplantation with untested relapsed disease have similar DFS when compared with patients with chemotherapy-sensitive relapse [23]; another study found similar results with chemotherapy-resistant relapse [22]. There is evidence that treatment with 3 or more regimens prior to transplantation increases the risk of adverse outcomes. Salvage chemotherapy before SCT to determine chemotherapy sensitivity in relapsed patients, however, may help define patient prognosis. Some investigators assume that if there was a long duration of CR, then the disease is sensitive, and they proceed to SCT in untested relapse. The time interval between relapse and SCT is used variably to test for prognosis, to select for transplantation only patients with chemotherapy-sensitive disease, to locate a donor for allogeneic transplantation, or to allow time for insurance approval. There are no data to support or disprove the efficacy of testing relapsed disease for chemotherapy sensitivity before proceeding to SCT.

Table 7. *Grading Summary of the Evidence for SCT in Chemotherapy-Resistant Relapsed/Primary Refractory Disease**

Reference	Quality of Evidence†	Strength of Evidence†			Median Follow-up, mo	No. of Patients	ALCL	IWF F/G/H
		OS	EFS	DFS				
Armitage et al. [20]	2-3	NC	NC	NC	NS	29	0%	100%
Vose et al. [21]	2-1	NC	NC	NA	32	25	0%	88%
Saez et al. [22]	2-1	NC	NA	NC	56	33	0%	F/G 91%
						10		H 50%
Mills et al. [23]	2-3	NC	NC	NC	29	107	0%	85%
Stiff et al. [24]	2-1	NC	NC	NA	NS	94	0%	76%
Santini et al. [25]	2-1	NC	NC	NC	37	54	4%	89%
Wheeler et al. [26]	2-1	NC	NA	NC	19	70	0%	83%
Gribben et al. [27]	2-1	NC	NA	NA	NS	50	0%	82%
Gulati et al. [28]	2-1	NC	NA	NC	42	44	0%	70%
Philip et al. [29]	2-2	NC	NC	NC	33	100	0%	77%
Caballero et al. [30]	2-3	NC	NA	NC	NS	366	NS	80%
Horning et al. [31]	2-1	NC	NC	NC	30	72	0%	71%
Sehn et al. [32]	2-2	NC	NA	1	47	35	0%	100%
Popat et al. [33]	2-2	2	NA	2	32	90	0%	100%
Kewalramani et al. [34]	2-2	NC	NC	NA	35	NS	0%	84%
Mundt et al. [35]	2-1	NA	NA	NC	20	53	0%	93%
Vose et al. [36]	2-2	NA	1	NA	21	158	0%	84%
Petit et al. [37]	2-1	NC	NC	NC	NS	14	0%	86%
Donato et al. [38]	2-1	NA	NA	NA	NS	36	11%	81%
Haioun et al. [39]	2-1	NC	NC	NC	NS	NS	NS	71%
van Besien et al. [40]	2-2	NC	NA	NC	38	14	0%	93%
Gryn et al. [41]	2-1	NA	NA	NC	24	40	0%	100%

*SCT indicates hematopoietic stem cell transplantation; OS, overall survival; EFS, event-free survival; DFS, disease-free survival; ALCL, anaplastic large cell lymphoma; IWF, International Working Formulation; F, diffuse mixed cell; G, diffuse large cell; H, diffuse large cell immunoblastic; NC, no comparison in study between high-dose chemotherapy with SCT and standard chemotherapy; NA, not applicable; NS, not stated.

†See Tables 1 and 2 for definitions.

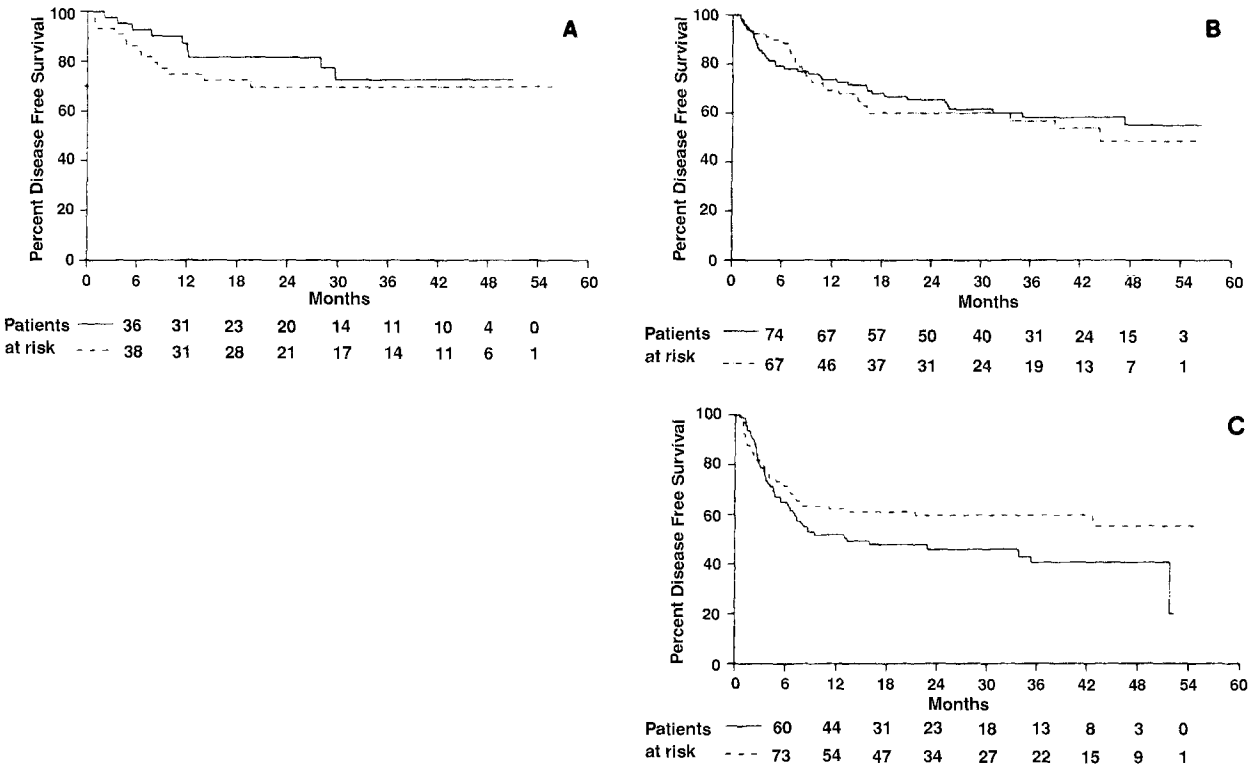

Figure 3. Estimated disease-free survival according to randomized consolidation procedure for the 3 risk subgroups defined by age-adjusted International Index. A, Low-risk group (P = .42). B, Low-to-intermediate–risk group (P = .63). C, High-to-intermediate–risk and high-risk groups (P = .07). Of those who received sequential chemotherapy (—), patients at risk were n = 43 (A), n = 96 (B), and n = 95 (C); relapses or deaths were n = 9 (A), n = 38 (B), and n = 52 (C); 3-year estimates of patients at risk were 73% (A), 58 % (B), and 41% (C). Of those who underwent autologous bone marrow transplantation (-----), patents at risk were n = 44 (A), n = 78 (B), and n = 108 (C); relapses or deaths were n = 13 (A), n = 32 (B), and n = 42 (C); 3-year estimates were n = 70% (A), n = 56% (B), and 60% (C). Reprinted with permission from Haioun C, Lepage E, Gisselbrecht C, et al. Comparison of autologous bone marrow transplantation with sequential chemotherapy for intermediate-grade and high-grade non-Hodgkin's lymphoma in first complete remission: a study of 464 patients. Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol.* 1994;12(12):2543-2551.

V. FIRST COMPLETE REMISSION AFTER FULL-COURSE STANDARD INDUCTION THERAPY

Two pilot studies demonstrated the feasibility of performing BMT in DLCL patients in first CR [42,43]. The LNH87-2 randomized multicenter study by Haioun et al. enrolled 1043 patients under age 55 with newly diagnosed intermediate- or high-grade NHL who met at least one of the following criteria: ECOG performance status 2 to 4, ≥2 extranodal sites, tumor burden of ≥10 cm in largest dimension, BM or central nervous system (CNS) involvement, and Burkitt or lymphoblastic subtypes with no BM or CNS involvement [44-46]. A total of 916 eligible patients received standard induction chemotherapy. Among these patients, 520 achieved CR, and 464 were randomized to receive high-dose therapy with CBV followed by autologous BMT (n = 230) or sequential chemotherapy with ifosfamide, etoposide, asparaginase, and cytarabine (n = 234). At median follow-up of 28 months, there was no statistically significant difference in the 3-year OS (71% chemotherapy versus 69% BMT; P = .60) or DFS (52% chemotherapy versus 59% BMT; P = .46 [Figure 3]) [44].

Two subsequent publications presented a retrospective, unplanned subset analysis of the 236 high-intermediate/high–risk IPI patients who achieved CR after induction therapy and were randomized. At median follow-up of 54 months in this subset, there was a statistically significant benefit in the BMT arm with respect to DFS but not OS (P = .06 benefiting the BMT arm [Figure 4]) [45]. Furthermore, at a median follow-up of 8 years, patients in the BMT arm had higher rates of DFS (55% versus 39%; P = .02) and OS (64% versus 49%; P = .04 [Figure 5]) [46] compared with patients who received sequential chemotherapy without BMT.

Stahel et al. performed a prospective multicenter trial of risk-adapted therapy for DLCL patients [47]. High-risk criteria (defined in 1991 before the IPI) included DLCL stage III to IV or mediastinal DLCL stage II to IV, and an elevated LDH level, and/or 1 lesion >10 cm. Patients with high-risk DLCL in first CR (n = 31) after etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (VACOP-B) × 12 were treated with CBV conditioning and autologous PBSCT or BMT. Patients with low-risk DLCL received VACOP-B × 12 followed by involved field radiotherapy as consolidation (n = 51). Twenty-nine percent of the high-risk group did not receive SCT or BMT as intended because of insufficient response to VACOP-B (n = 6), patient refusal (n = 2), pulmonary toxicity to VACOP-B (n = 1) and death during VACOP-B (n = 1). Of the high-risk group, 84% were identified retrospec-

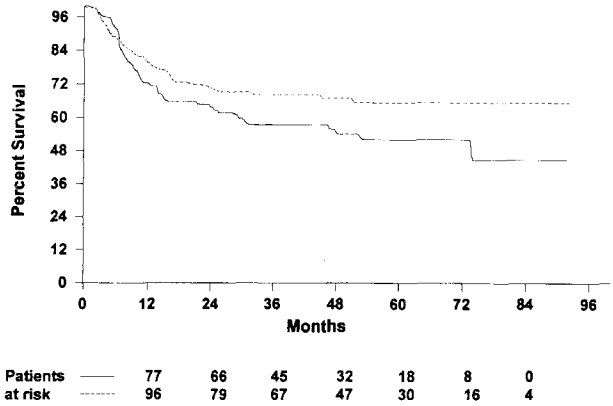

Figure 4. Estimated survival according to randomized consolidation procedure for high-intermediate– and high-risk patients. Of those who received sequential chemotherapy (——), patients at risk were n = 111; the 5-year estimate was 52%. Of those who underwent autologous bone marrow transplantation (-----), patients at risk were n = 125; 5-year estimate was 65%. P = .06. Reprinted with permission from Haioun C, Lepage E, Gisselbrecht, et al. Benefit of autologous bone marrow transplantation over sequential chemotherapy in poor-risk aggressive non-Hodgkin's lymphoma: updated results of the prospective study LNH87-2. Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol.* 1997;15:1131-1137.

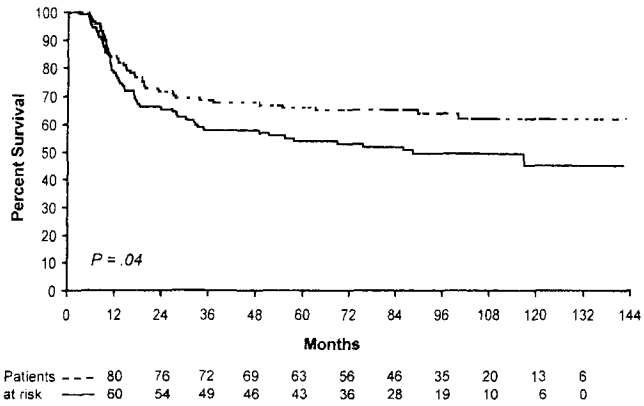

Figure 5. Estimated survival according to randomized consolidation procedure for the high-intermediate– and high-risk patients. Of those who received sequential chemotherapy (——), patients at risk were n = 111; 8-year estimate was 49%. Of those who underwent autologous bone marrow transplantation (-----), patients at risk were n = 125; 8-year estimate was 64%. P = .04. Reprinted with permission from Haioun C, Lepage E, Gisselbrecht C, et al. Survival benefit of high-dose therapy in poor-risk aggressive non-Hodgkin's lymphoma: final analysis of the prospective LNH87-2 Protocol. A Groupe d'Etude des Lymphomes des l'Adulte study. *J Clin Oncol.* 2000;18:3025-3030.

tively as high-intermediate/high–risk IPI; of the low-risk group, 96% were identified as low/low-intermediate–risk IPI. At median follow-up of 46 months, the 3-year EFS was 76% for the low-risk and 55% for the high-risk group (P = .061) by intent-to-treat analysis. OS was significantly higher in the low-risk group (83% versus 53%; P = .005).

A retrospective cohort study by Bouabdallah et al. found that 60 patients treated with BMT in first CR or PR had a significantly improved OS, DFS, and EFS when compared with 66 standard chemotherapy patients [48]. At a median follow-up of 63 months, patients in the BMT group had a significantly higher 5-year OS (76% versus 31%; P < .0001), EFS (64% versus 24%; P < .0001) and DFS (76% versus 42%; P = .002) compared with the standard chemotherapy group. The patients were well-matched based on lymphoma histology, sex, performance status, Ann Arbor (AA) stage, and IPI. The standard chemotherapy group, however, had a higher proportion of patients with an elevated LDH level (82% versus 63%; P = .01) and older age (median 51 years versus 43 years; P = .02), both of which are known poor prognostic factors.

The Evidence for Transplantation in First Complete Remission

There are no prospective studies comparing the conditioning regimens, stem cell mobilization techniques, stem cell source, or donor type for DLCL patients in first CR. The trial by Haioun et al. [44-46] used CBV as the conditioning regimen, stem cells harvested from BM, and autologous donors. This work provides the only evidence of SCT in first CR that has been methodologically evaluated in comparison to standard chemotherapy regimens. It is not known if outcomes in first CR, high-intermediate/high–risk IPI DLCL patients might be improved using allogeneic donors, nonmyeloablative or alternative conditioning and/or stem cell mobilization regimens, or immunotherapy following transplantation. These are areas of possible future research.

The evidence for SCT in first CR is summarized in Table 8.

VI. ABBREVIATED STANDARD INDUCTION THERAPY (<6 COURSES OF CHOP OR <12 COURSES OF VACOP-B OR MACOP-B)

Gherlinzoni et al. performed a multicenter randomized trial comparing methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B) × 12 (n = 75) versus MACOP-B × 8 followed by autologous SCT with BEAC conditioning (n = 75) as front-line therapy [49]. Eligible patients had 2 or 3 risk factors by age-adjusted IPI (Aa-IPI). The interval between the end of MACOP-B × 8 and SCT was less than 4 weeks. Forty percent (30/75) of the patients did not undergo SCT as planned, primarily due to disease progression. By intent-to-treat analysis, there was no significant difference between the 2 groups with respect to PFS, relapse-free survival, or OS.

Verdonck et al. randomized 69 patients with no BM involvement and a PR after 3 courses of induction with CHOP to receive either 5 additional courses of CHOP (n = 35) or autologous BMT (n = 34) with CT conditioning [50]. PR was defined as a reduction by at least 25% of the sum of the largest tumor diameters. Only 1 patient in each study arm was in the high-risk IPI group; 56% of patients in each study arm were at low or low-intermediate IPI risk. At

Table 8. *Grading Summary of the Evidence for SCT in First Complete Remission**

Reference	Quality of Evidence†	Strength of Evidence†			Median Follow-up, mo	No. of Patients	ALCL	IWF F/G/H
		OS	EFS	DFS				
Gaspard et al. [42]	2-1	NC	NC	NC	15	15	0%	80%
Nademanee et al. [43]	2-1	NC	NC	NC	34	20	0%	70%
Haioun et al. [44]	1	3	3	3	28	464	8%	69%
Haioun et al. [45]	1	2	NA	1	54	236	9%	73%
Haioun et al. [46]	1	1	NA	1	96	236	9%	73%
Stahel et al. [47]	2-1	1	2	NA	46	82	12%	76%
Bouabdullah et al. [48]	2-2	1	1	1	63	126	16%	73%

*SCT indicates hematopoietic stem cell transplantation; OS, overall survival; EFS, event-free survival; DFS, disease-free survival; ALCL, anaplastic large cell lymphoma; IWF, International Working Formulation; F, diffuse mixed cell; G, diffuse large cell; H, diffuse large cell immunoblastic; NC, no comparison in study between high-dose chemotherapy with SCT and standard chemotherapy; NA, not applicable.

†See Tables 1 and 2 for definitions.

median follow-up of 3 years, there was no significant difference between the CHOP and BMT groups with regards to rate of CR (74% versus 68%), 4-year DFS (72% versus 60%), 4-year EFS (53% versus 41% [Figure 6]), or 4-year OS (85% versus 56%).

In a companion study to the Verdonck et al. clinical trial, Uyl-de Groot et al. simultaneously collected economic data comparing the costs associated with autologous BMT with the costs of standard chemotherapy [51]. The mean costs associated with standard chemotherapy in the treatment period were significantly less than those in the BMT group (US $3,118 versus US $34,447; $P < .01$), but the average costs in the 2-year follow-up period were not significantly different between the groups (standard chemotherapy, US $12,436 versus BMT, US $15,837; P = NS). A comparison of long-term costs in a follow-up period of 8 years found higher but not statistically significant costs associated with BMT (US $56,512) compared to standard chemotherapy (US $20,397). The discounted life years (LYs) and quality-adjusted life years (QALYs) for BMT (LYs, 4.49; QALYs, 3.84) were lower than for standard chemotherapy (LYs, 5.04; QALYs, 4.33).

Martelli et al. performed a multicenter randomized trial comparing conventional full-course induction chemotherapy (MACOP-B × 12 weeks) with a similar but abbreviated induction regimen followed by PBSCT (MACOP-B × 8 weeks, autotransplantation with BEAC conditioning) [52]. All 109 newly diagnosed patients had 2 to 3 risk factors by age-adjusted IPI. Preliminary intent-to-treat analysis at median follow-up of 25 months demonstrated no statistically significant difference in OS or PFS between the full-course induction chemotherapy arm and the abbreviated induction/PBSCT arm. Nearly half of the patients (46%) randomized to the abbreviated induction/PBSCT arm did not receive transplants due to progressive disease (33%), prior toxicity (38%), or patient refusal (29%). This study continues to accrue patients; forthcoming analyses with additional patients and more mature follow-up are anticipated.

A multicenter study by Reyes et al. did not meet this review's criterion of including 70% DLCL patients (69% of patients were DLCL). The study is noteworthy, however, for also evaluating an abbreviated induction course and autotransplantion compared to a more standard regimen [53]. Poor-risk intermediate- or high-grade NHL patients were randomized to receive either full-course induction therapy with ACVB (doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisolone) followed by sequential consolidation, or an abbreviated induction regimen followed by PBSCT with BEAM conditioning. The abbreviated induction regimen consisted of 1 cycle of CEOP (cyclophosphamide, epirubicin, vincristine, and prednisone) and 2 cycles of ECVBP (epirubicin, cyclophosphamide, vindesine, bleomycin, and prednisone). Analysis of 370 eligible patients at median follow-up of 30 months showed a significantly better 3-year EFS (54% versus 41%; $P = .01$) and OS (63% versus 47%; $P = .003$) for the conventional chemotherapy group compared to the abbreviated induction/PBSCT group. There was no significant difference in CR or treatment-related mortality between the 2 groups. Of patients randomized to the abbreviated induction/PBSCT group, 29% did not proceed to transplantation, primarily due to disease progression.

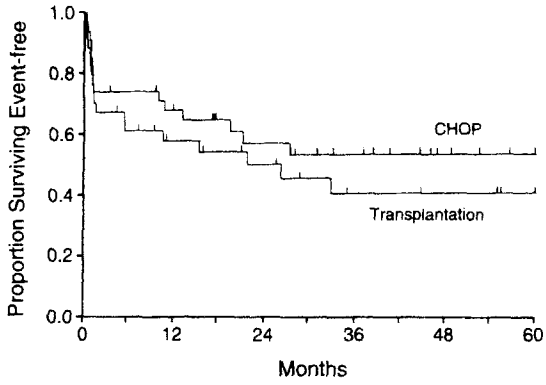

Figure 6. Event-free survival from the time of randomization, according to treatment group. Among 35 patients assigned to receive 8 courses of CHOP and 34 patients assigned to receive high-dose chemoradiotherapy and autologous bone marrow transplantation, there were 15 and 18 treatment failures, respectively. Reprinted with permission from Verdonck LF, van Putten WLJ, Hagenbeek A, et al. Comparison of CHOP chemotherapy with autologous bone marrow transplantation for slowly responding patients with aggressive non-Hodgkin's lymphoma. *N Engl J Med.* 1995;332:1045-1051.

Intragumtornchai et al. randomized DLCL patients under age 55 (65% were high-risk AaIPI) after 3 courses of CHOP to receive either continued CHOP therapy (n = 25) or 2 to 4 courses of ESHAP followed by PBSCT (n = 23) [54]. At median follow-up of 12 months, the PBSCT group had significantly higher rates of freedom from progression (FFP) (64% versus 25%; P = .008), freedom from relapse (91% versus 37%; P = .05) and EFS (33% versus 13%; P = .05) compared to the CHOP group. There was no significant difference between the 2 groups in OS (34% versus 32%; P = 0.83).

The evidence for SCT after abbreviated induction therapy is summarized in Table 9.

VII. MIXED DISEASE RESPONSES TO INDUCTION THERAPY

Santini et al. randomized newly diagnosed, untreated patients with stage II bulky (≥10 cm), stage III, or stage IV diffuse intermediate- or high-grade NHL to receive either VACOP-B for 12 weeks followed by DHAP as a salvage regimen (n = 61) or VACOP-B for 12 weeks followed by autologous BMT with BEAM conditioning (n = 63) [55]. Patients proceeded to BMT regardless of response to VACOP-B. All results were presented as intent-to-treat analyses. At median follow-up of 42 months, there was no significant difference between the groups in response rate or in 6-year DFS, PFS, or OS (Figure 7). Of patients randomized to the BMT arm, 29% did not undergo the procedure due to ineligibility, death during induction, patient refusal, or disease progression. Retrospective analysis by IPI showed a significantly improved 6-year DFS (87% versus 48%; P = .008) and a trend toward improved 6-year PFS (65% versus 37%; P = .08) for high-intermediate– and high-risk IPI groups in the BMT arm, with no difference in 6-year OS (65% versus 65%; P = .5) compared to patients in the non-BMT arm.

Fanin et al. compared outcomes of autologous SCT among patients in the 3 major subtypes of DLCL (centroblastic, immunoblastic, and anaplastic), and by disease status at the time of transplantation [56]. The following characteristics were seen among 797 patients: 53.5% had low- or low-intermediate–risk IPI; first CR 27.7%, ≥ second CR 17.3%; PR 26.1%; sensitive relapse 8.7%; relapse/refractory 15%. Significant prognostic factors by multivariate analysis for PFS were disease status at SCT (P < .0001) and IPI score (P < .008). Histology subtype (centroblastic versus immunoblastic versus anaplastic), stage, B symptoms, age, sex, and conditioning regimen were not significant predictors of PFS.

Conde et al. reported on 39 patients who underwent transplantations for mediastinal DLCL with sclerosis [57]. Seven patients had BMT; 32 had PBSCT. Conditioning regimens were BEAM (n = 16), BEAC (n = 11), CT (n = 5), and others (n = 7). The OS by disease status at time of SCT was first CR, 78%; second CR, 75%; stable disease, 47%; resistant disease, 12%. Median time to relapse was 7.5 months.

The Evidence for Transplantation Irrespective of Disease Status

Allogeneic BMT

Dhedin et al. studied a group of 73 patients (71% DLCL) who underwent allogeneic BMT from an HLA-matched sibling or (in 1 patient) an HLA-matched unrelated donor [58]. Ten patients had a prior autologous BMT and the median number of prior therapies was 2. Among all patients, 34% were in CR ≥1, 29% were in PR ≥1, and 37% had refractory disease. At median follow-up of 90 months, the 5-year OS and PFS were 41% and 40%, respectively. A total of 16 patients relapsed, all in the first 15 months, except 1 patient who relapsed at 7 years post-BMT. Multivariate analysis of factors predictive for survival found that patients who received fewer than 3 pretransplantation chemotherapy regimens (relative risk [RR] = 20.8; P = .04) and were in CR at time of BMT (RR = 4.043; P < .0001) had significantly prolonged survival. Patients who underwent transplantations while in CR had a lower risk of disease progression post-BMT (P = .01) and fewer toxic deaths (P = .01) compared with patients who were not in CR at time of BMT. Five-year OS in 25 patients who underwent transplantations while in CR was 76% compared with 23% in 48 patients not in CR at BMT (P < .0001). Age, sex, BM or CNS involvement at diagnosis, disease stage at diagnosis, immunophenotype, prior autologous BMT, response to induction therapy, BM involvement at time of transplantation, and disease sensitivity at time of transplantation were not significant predictors of survival by multivariate analysis.

The Role of BM Involvement

Bolwell et al. retrospectively reviewed 147 DLCL patients who underwent PBSCT to compare outcomes of patients with and patients without bone marrow involvement [59]. No BM involvement during disease course was

Table 9. *Grading Summary of the Evidence for SCT After Abbreviated Induction Therapy**

Reference	Quality of Evidence†	Strength of Evidence†			Median Follow-up, mo	No. of Patients	ALCL	IWF F/G/H
		OS	EFS	DFS				
Gherlinzoni et al. [49]	I	NC	NC	3	34	150	9%	77%
Verdonck et al. [50]	I	3	3	3	36	69	0%	71%
Martelli et al. [52]	I	3	NC	3	25	109	14%	73%
Reyes et al. [53]	I	5	5	NC	30	370	NS	69%
Intragumtornchai et al. [54]	4	3	I	I	12	58	NS	78%

*SCT indicates hematopoietic stem cell transplantation; OS, overall survival; EFS, event-free survival; DFS, disease-free survival; ALCL, anaplastic large cell lymphoma; IWF, International Working Formulation; F, diffuse mixed cell; G, diffuse large cell; H, diffuse large cell immunoblastic; NC, no comparison in study between high-dose chemotherapy with SCT and standard chemotherapy; NS, not stated.

†See Tables 1 and 2 for definitions.

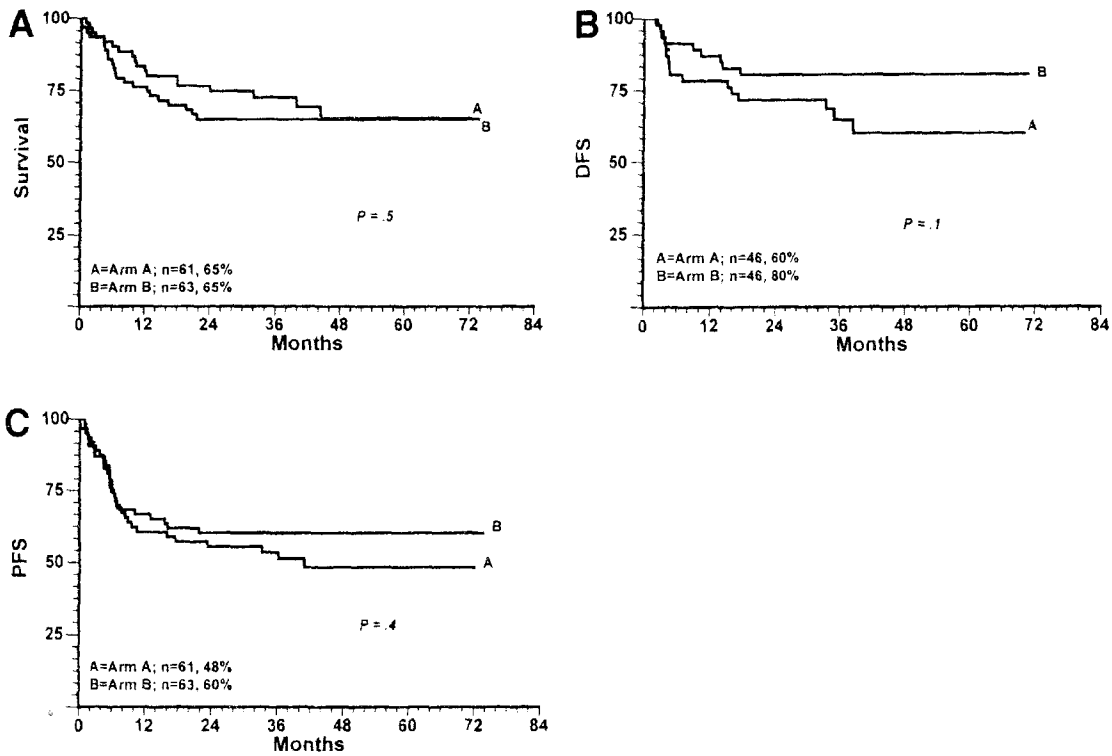

Figure 7. Estimated 6-year overall survival, disease-free survival (DFS), and progression-free survival (PFS) according to treatment arm (arm A, VACOP-B [etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin]; arm B, VACOP-B plus ABMT). Reprinted with permission from Santini G, Salvagno L, Leoni P, et al. VACOP-B versus VACOP-B plus autologous bone marrow transplantation for advanced diffuse non-Hodgkin's lymphoma: results of a prospective randomized trial by the non-Hodgkin's lymphoma cooperative group. *J Clin Oncol.* 1998;16:2796-2802.

seen in 113 patients (77%); 16 patients (11%) had BM involvement at diagnosis only; 5 patients (3%) had BM involvement at time of SCT only; and 13 patients (9%) had BM involvement at both time of diagnosis and time of transplantation. Four-year OS and EFS were not significantly different between these groups (Table 10). By multivariate analyses, elevated LDH level (P = .002), refractory disease (P = .04), and >1 course of prior chemotherapy (P = .05) were the only significant predictors of OS and EFS. BM involvement was not a significant predictor for OS and EFS when assessed by whether there was ever BM involvement as well as by time of BM involvement.

Evidence for SCT irrespective of disease response to induction therapy is summarized in Table 11.

VIII. UP-FRONT HIGH-DOSE INDUCTION THERAPY IN NEWLY DIAGNOSED UNTREATED PATIENTS

A. High-Dose Sequential Therapy in High-Intermediate/High–Risk IPI Patients

In a multi-institution study, Gianni et al. randomized 98 patients with no BM involvement and a high-intermediate– or high-risk IPI to receive either MACOP-B (n = 50) or high-dose sequential (HDS) therapy (n = 48) [60]. A cross-over study design allowed patients who failed one treatment to receive subsequent treatment with the other. Patients in the MACOP-B arm received a 12-week course. HDS patients received a 4-phase treatment schedule consisting of a 21-day induction regimen, stem cell mobilization with high-dose cyclophosphamide plus a colony-stimulating factor, followed by BM and/or PBSC collections, and a 4-day consolidation phase. Lastly, SCT was performed with either TBI, etoposide, and melphalan (n = 30); or mitoxantrone, etoposide, and melphalan (n = 18) as conditioning. The HDS therapy arm had a significantly better 7-year EFS than the MACOP-B arm (76% versus 49%; P < .004 [Figure 8]). The 7-year OS in the HDS therapy arm showed a trend toward a significant difference when compared to the MACOP-B arm (81% versus 55%, P = .09).

Vitolo et al. reported an ongoing multicenter trial of HDS therapy plus autologous SCT (n = 46) compared with an intensified regimen of MegaCEOP (cyclophosphamide [1200 mg/m^2] epirubicin [110 mg/m^2], vincristine [1.4 mg/m^2], and prednisone [40 mg/m^2]) (n = 53) in DLCL patients [61]. Of the patients, 65% had an high-intermedi-

Table 10. *Summary of Overall and Event-Free Survival by Bone Marrow Involvement [59]**

BM Involvement	4-year OS (P = .29)	4-year EFS (P = .42)
Never	52%	40%
At SCT	80%	80%
At Diagnosis	74%	47%
Both	83%	61%

*BM indicates bone marrow; OS, overall survival; EFS, event-free survival; SCT, hematopoietic stem cell transplantation.

Table 11. *Grading Summary of the Evidence for SCT Irrespective of Disease Response to Induction Therapy**

Reference	Quality of Evidence†	Strength of Evidence†			Median Follow-up, mo	No. of Patients	ALCL	IWF F/G/H
		OS	EFS	DFS				
Santini et al. [55]	I	3	NA	3	42	124	10%	83%
Fanin et al. [56]	2-2	NC	NC	NC	NS	420	12%	88%
Conde et al. [57]	2-2	NC	NC	NC	20	39	NS	100%
Dhedin et al. [58]	2-3	NC	NA	NC	90	73	18%	71%
Bolwell et al. [59]	2-2	NC	NC	NC	NS	147	NS	100%

*SCT indicates hematopoietic stem cell transplantation; OS, overall survival; EFS, event-free survival; DFS, disease-free survival; ALCL, anaplastic large cell lymphoma; IWF, International Working Formulation; F, diffuse mixed cell; G, diffuse large cell; H, diffuse large cell immunoblastic; NC, no comparison in study between high-dose chemotherapy with SCT and standard chemotherapy; NS, not stated.

†See Tables 1 and 2 for definitions.

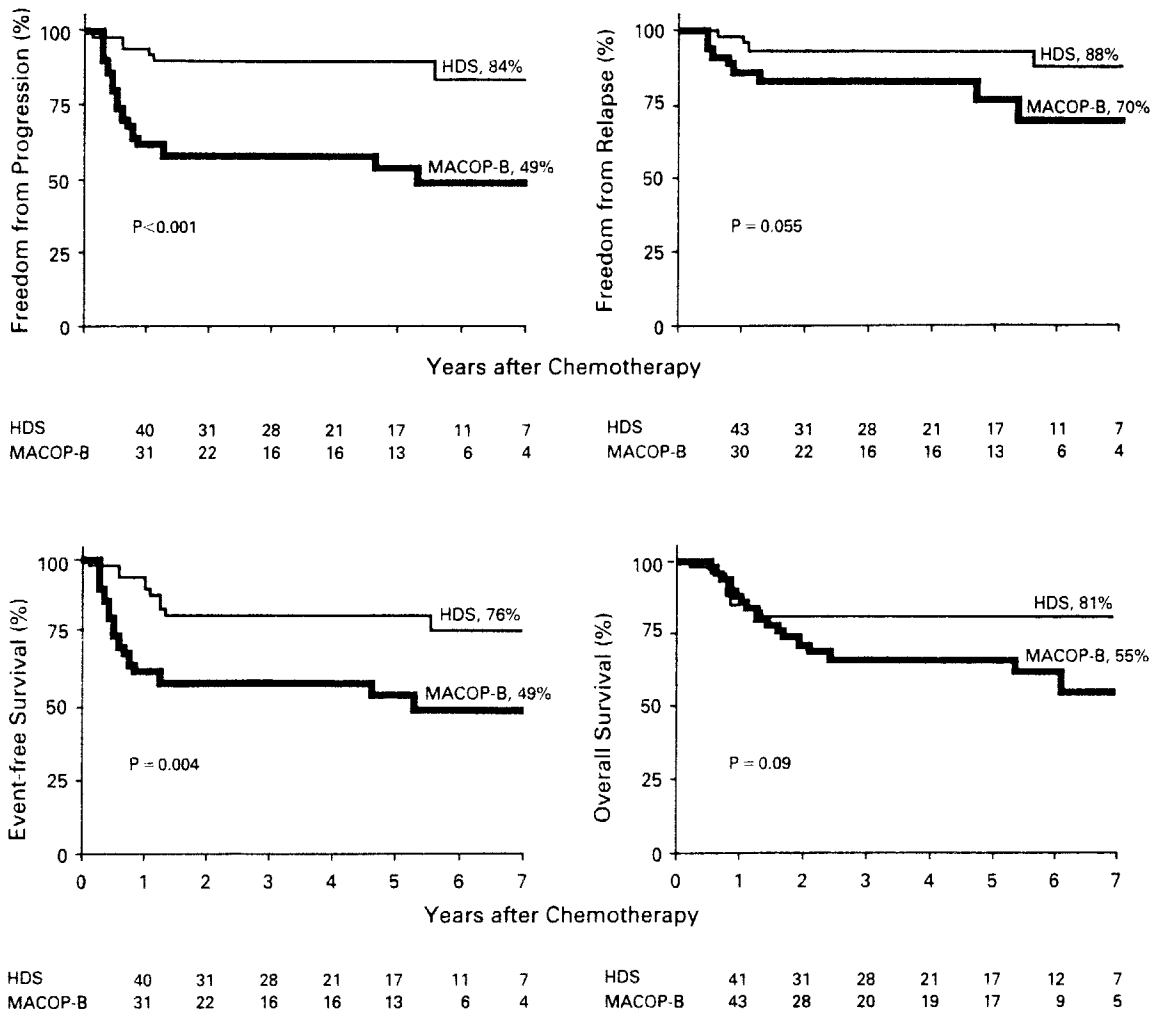

Figure 8. Kaplan-Meier plots of freedom from disease progression, freedom from relapse, event-free survival, and overall survival for 48 patients initially assigned to high-dose sequential therapy (HDS) and 50 assigned to MACOP-B. The initial number of patients in complete remission and at risk for relapse was 46 for HDS and 35 for MACOP-B. The median follow-up was 55 months. The number of patients at risk is shown below each time point. Percentages at right are for each category of survival (free from disease progression, free from relapse, event-free, and overall) at 7 years. Reprinted with permission from Gianni AM, Bregni M, Siena S, et al. High-dose chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma. *N Engl J Med.* 1997;336:1290-1297. Copyright © 1997 Massachusetts Medical Society. All rights reserved.

ate–risk IPI score and 35% had a high-risk–IPI score. The HDS regimen consisted of adriamycin, vincristine, and prednisone followed by intensification with cyclophosphamide, methotrexate, vincristine, and etoposide with or without 2 DHAP courses in patients with BM involvement. The HDS regimen was followed by autologous SCT conditioned with mitoxantrone and melphalan. MegaCEOP was given for 6 courses in BM-negative patients and for 8 courses in BM-positive patients. One patient in the HDS/SCT arm and 2 in the MegaCEOP arm died of toxicity. Six patients in the HDS/SCT arm and 5 in the MegaCEOP arm did not complete therapy due to toxicity or progression. Similar rates of CR were observed in both groups; however, patients with high-risk IPI had a significantly lower rate of CR than those with high-intermediate–risk IPI (49% versus 69%; $P < .02$). This study closed to accrual in December 1999 and is ongoing for survival analyses.

Cortelazzo et al. assessed 2 consecutive cohorts of previously untreated DLCL patients younger than 60 years of age to compare MACOP-B × 12 (n = 60) with MACOP-B × 8, 1 to 2 cycles of mitoxantrone, cytarabine, and dexamethasone (MAD) intensification and PBSCT or BMT with BEAM conditioning (n = 61) [62]. Therapy was completed by 85% of the patients in each group. Median follow-up of surviving patients was 37 months for the transplantation cohort and 87.5 months for the standard chemotherapy cohort. By intent-to-treat analysis, the transplantation group had a higher rate of response (CR/CR with scan abnormalities of unknown significance [CRu]) (84% versus 68%; $P = .0491$); a better 2-year EFS (70% versus 50%; $P = .0281$) and no difference in 2-year OS (73% versus 62%; $P = .2191$) compared with the standard chemotherapy group.

A retrospective analysis by AaIPI demonstrated a significant difference in the 2-year EFS (63% transplantation versus 40% chemotherapy group; $P = .0269$) in the high-intermediate/high–risk IPI subgroup, but no difference (2-year EFS, 85% transplantation versus 82% chemotherapy group; $P = .8297$) in the low-intermediate/low–risk IPI subgroup.

Vitolo et al. conducted a phase II study of 50 DLCL patients [63] who are an overlapping population with the Cortelazzo et al. transplantation cohort [62]. The 3-part HDS therapy schema consisted of MACOP-B induction for 8 weeks, intensification with MAD plus G-CSF, followed by leukapheresis and autologous PBSCT with BEAM as conditioning. BM involvement was seen in 38% of the patients. At 32 months, OS was 56% and failure-free survival (FFS) was 50%. There was a trend toward better survival rates in patients who did not have BM involvement compared with those who did (3-year OS, 58% versus 53%; 3-year FFS, 52% versus 45%).

Stoppa et al. conducted a pilot phase II trial in 20 untreated DLCL patients younger than 60 years of age with 2 to 3 IPI factors using 6 HDS therapy courses [64]. Each of the first 3 courses consisted of 1 cycle of CHOP followed by PBSC collection. Each of the last 3 courses consisted of 1 cycle of CHOP plus etoposide and cisplatin followed by reinfusion of PBSCs. Of 20 patients, 17 completed all 6 courses; 1 patient died of toxicity during the 6-course schedule. The response rate after 6 courses was 85% (65% CR; 20% PR). At median follow-up of 31 months, 2-year OS was 73%, FFS was 56%, and DFS was 86%.

B. High-Dose Sequential Therapy in Non–IPI High-Risk Patients

Milpied et al. performed a randomized trial in newly diagnosed patients with low- (7%), low-intermediate (38%), high-intermediate– (48%) and high- (7%) risk IPI patients under age 60 [65]. Results of 8 cycles of CHOP every 21 days were compared with those of an HDS therapy regimen consisting of CEEP (cyclophosphamide, epirubicin, vindesine, and prednisone) for 2 cycles every 15 days with granulocyte macrophage colony–stimulating factor (GM-CSF) support, PBSC collections after the first or second course of CEEP, followed by 1 course of high-dose methotrexate and cytarabine, and PBSCT with BEAM conditioning.

In an intent-to-treat analysis at 22-month median follow-up, OS was 51% for CHOP versus 76% for PBSCT ($P > .1$); EFS was 38% for CHOP versus 59% for PBSCT ($P = .03$) and FFP was 40% for CHOP versus 60% for PBSCT ($P = .05$). Subanalysis showed a better OS in high-intermediate–risk IPI patients in the PBSCT arm (3-year OS, 78% versus 43%; $P = .01$).

A feasibility study of a 3-phase HDS therapy trial for 40 patients with BM involvement was performed by Santini et al. [66]. Half of the patients had a low-intermediate–risk IPI score (1 factor). Patients were given induction therapy with VACOP-B × 8, intensification with high-dose cyclophosphamide and G-CSF followed by leukapheresis, and autologous PBSCT with BEAM or melphalan plus TBI as the conditioning regimen. The 5-year OS for the 40 HDS therapy patients was 42%; the DFS and FFS were 39% and 34%, respectively.

The Evidence for Transplantation in Newly Diagnosed Untreated Patients

Double/Tandem Autotransplantations. There have been 2 pilot studies of double autotransplantations in high-risk DLCL patients [67-69]. Haioun et al. enrolled 37 patients younger than 60 years with 2 or 3 age-adjusted IPI factors in a study consisting of induction with ACVB × 4, followed by leukapheresis with G-CSF in patients who responded after the fourth ACVB cycle or after an additional mobilization regimen (cyclophosphamide, etoposide, and G-CSF) [67]. A first PBSCT used mitoxantrone, cyclophosphamide, etoposide and BCNU conditioning in 24 responding patients for a median of 4 months after start of induction, followed by a second PBSCT using busulfan, melphalan, and carboplatin in 19 patients for a median of 2 months after the first autotransplantation. Of 19 patients who completed both transplantations, 1 died from early toxicity (veno occlusive disease), 1 progressed immediately after second transplantation, 1 was in PR, and 16 were in CR. Four of the responders have relapsed and 2 others have died of treatment-related toxicity 3 to 5 months after the second PBSCT. A total of 11 patients (58%) remain in CR at 9 to 19 months post-SCT.

Clavio and Ballestrero et al. performed a feasibility study of a 3-step regimen [68,69]. DLCL patients (N = 30) with high-intermediate– (n = 13) or low-intermediate–risk (n = 17) IPI received high-dose cyclophosphamide and GM-CSF, or G-CSF followed by 2 to 4 leukaphereses. Transplantations were performed as first-line therapy in 10 patients; consolidation after conventional dose therapy in

12; at relapse in 4; and with refractory disease in 4. All patients completed both transplantations. Mitoxantrone and melphalan were used as conditioning for first transplantation; etoposide and carboplatin were used for the second. At median follow-up of 3 years, 18 of 22 (82%) patients in the first line/consolidation group were alive and disease-free compared to 2 of 8 (25%) in the relapse/refractory group. Three patients died of relapsed or progressive disease; there were no deaths due to regimen-related toxicity.

The evidence for SCT as up-front HDS in newly diagnosed patients is summarized in Table 12.

IX. RESPONSE CRITERIA

A National Cancer Institute (NCI)-sponsored International Workshop was held in 1999 to standardize response criteria for NHL [70]. The results of the evidence-based review of DLCL presented here emphasize the importance of using standard criteria for measuring response to therapy in NHL patients. Standardization allows for more meaningful comparisons among clinical trials. This international working group's study provided consensus definitions of CR, CRu, PR and Relapse/Progression and included definitions of normal lymph node size, bone marrow assessment, and endpoints for clinical trials (eg, OS, EFS, PFS).

X. TREATMENT RECOMMENDATIONS

Treatment recommendations are outlined in Tables 13 and 14.

XI. FUTURE DIRECTIONS

A. New Molecular Subgroups and Prognostic Markers

Attempts to divide DLCL into molecular subtypes have not been successful. Both the REAL [1] and WHO [2] classifications found incomplete evidence that division by DLCL subtype would point to different therapeutic options and/or lead to better outcomes. Several recent abstracts and a manuscript have further explored the area of molecular analyses for the identification of new prognostic markers and possible new subtypes of DLCL. These molecular analyses were conducted in newly diagnosed patients who were subsequently followed for varying lengths of time after standard chemotherapy or high-dose chemotherapy with SCT.

The following molecular classifications have been found to be significant prognostic factors for survival independent of the IPI: germinal center expressing B cells (by DNA microarray technology) [71]; gene expression profiles, including genes related to cell origin; cell adhesion; apoptosis; RAS signaling; serine/threonine phosphorylation and tumor immunity (by oligonucleotide microarray technology) [72]; bcl-6 mutations [73]; lack of co-expression of bcl-2 and P-glycoprotein [74]; lack of survivin (an apoptosis inhibitor) expression [75]; low serum β2-microglobulin [76,77]; and bcl-2 protein expression [78,79]. Factors evaluated that were not significant predictors independent of the IPI were low serum CD44 [80], p53 mutation and p53 protein expression [81], number of cytogenetic aberrations [82], MIB-1 monoclonal antibody against Ki-67 nuclear protein [83], bcl-2 gene expression [78,79], and bcl-6 and MYC gene rearrangements [79]. It is likely that DLCL patients will be stratified by molecular classifications for clinical prognosis once there is better understanding of DLCL subtype gene expression.

B. Additional Ongoing Studies

Transplantation Versus Standard Chemotherapy.

The Scotland and Newcastle Group are conducting a phase III randomized trial of high-dose chemotherapy and radiotherapy plus autologous BMT in patients with aggressive NHL (Protocol ID: SNLG-NHL-V(a), EU-98032). Eligible patients under age 65 are stratified by risk group (good versus intermediate versus poor) as defined by the investigators.

Patients enrolled in the study undergo leukapheresis for the collection of autologous stem cells before induction chemotherapy. Patients receive induction therapy with CHOP or VAPEC-B (vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, and bleomycin) followed by radiation therapy to areas of original bulk or resid-

Table 12. *Grading Summary of the Evidence for SCT as Up-Front High-Dose Induction Therapy in Newly Diagnosed Patients**

Reference	Quality of Evidence†	Strength of Evidence†			Median Follow-up, mo	No. of Patients	ALCL	IWF F/G/H
		OS	EFS	DFS				
Gianni et al. [60]	I	2	I	I	55	98	0%	100%
Vitolo et al. [61]	I	NC	NC	NC	NS	99	0%	100%
Cortelazzo et al. [62]	2-2	I	3	NC	35	121	11%	77%
Vitolo et al. [63]	2-I	NC	NC	NC	32	50	12%	88%
Stoppa et al. [64]	2-I	NC	NA	NC	31	20	30%	70%
Milpied et al. [65]	I	3	I	2	22	168	NS	73%
Santini et al. [66]	2-I	NC	NC	NC	60	40	15%	85%
Haioun et al. [67]	2-I	NC	NC	NC	36	31	NS	78%
Ballestrero et al. [68]	2-I	NA	NC	NA	24	25	8%	92%
Clavio et al. [69]	2-I	NC	NA	NC	36	30	10%	90%

*SCT indicates hematopoietic stem cell transplantation; OS, overall survival; EFS, event-free survival; DFS, disease-free survival; ALCL, anaplastic large cell lymphoma; IWF, International Working Formulation; F, diffuse mixed cell; G, diffuse large cell; H, diffuse large cell immunoblastic; NC, no comparison in study between high-dose chemotherapy with SCT and standard chemotherapy; NA, not applicable.

†See Tables 1 and 2 for definitions.

Table 13. *Treatment Recommendations by Disease Response and International Prognostic Index (IPI) Risk* (Where Available)†*

Indication for SCT in:	Treatment Recommendation‡	Level of Evidence§	References‖	Comments
First chemotherapy-sensitive relapse	1	1	[8-11]	
Chemotherapy-resistant relapse/primary refractory disease	4	2	[22-34]	
First complete remission in patients with L/I-L IPI risk	3	1	[44]	Based on results from the original analysis with short follow-up
First complete remission in patients with H/I-H IPI risk	1¶	2	[44-46]	Refs [45-46] show a benefit for SCT based on a retrospective unplanned subset analysis in the high-risk patients only. Ref [44] demonstrates no benefit based on all randomized patients with short follow-up.
First partial remission after full-course induction therapy	4	NA		
After abbreviated induction therapy (<6 cycles of CHOP or <12 cycles of MACOP-B or VACOP-B)	3¶	1	[50-54]	Ref [50] used a unique definition of PR; Ref [52] is still accruing patients; Ref [53] significantly favors the standard chemotherapy arm, however included <70% DLCL.
As high-dose sequential therapy in untreated patients with I-H/H IPI risk	1	1	60	
As high-dose sequential therapy in untreated patients with L/L-I IPI risk	4¶	1	65	Only 45% of the patients had low or low-intermediate IPI risk; included 55% patients with high-intermediate or high IPI risk

*See Appendix B for definitions of IPI risk models.

†SCT indicates hematopoietic stem cell transplantation; L, low; I, intermediate; H, high; NA, no evidence available; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; MACOP-B, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin; VACOP-B, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin.

‡See Table 3 for definitions.

§See Table 1 for definitions. Levels 2-1 through 2-3 were condensed as Level 2 due to the heterogeneity of study designs represented by the references listed and for simplicity.

‖The references listed represent the highest level of evidence used to make the treatment recommendation and are not inclusive of all evidence described in the review.

¶Treatment recommendation is based on problems in methodology of the study(ies).

Table 14. *Treatment Recommendations for Transplantation Techniques**

Procedure Indicated	Treatment Recommendation†	Level of Evidence‡	References§	Comments
Double/Tandem SCT	4	2	[67-69]	Studies consisted of mixed population of untreated, relapsed, and refractory patients
Myeloablative allogeneic SCT	4	2	[40,58]	
Nonmyeloablative allogeneic SCT	4	NA		
Autologous BMT	1	1	[8-11,44-46]	
Autologous PBSCT	1	3		
Purging	4	2	18	
Stem cell mobilization method	4	2	[37-39]	
Conditioning regimens	4	NA		
As high-dose sequential therapy in patients with I-H/H IPI risk	1	1	[60]	
As high-dose sequential therapy in patients with L/L-I IPI risk	4	1	[65]	Only 45% of the patients had low or low-intermediate IPI risk; included 55% patients with high-intermediate or high IPI risk

*SCT indicates hematopoietic stem cell transplantation; NA, no evidence available; BMT, bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation; L, low; I, intermediate; H, high; IPI, International Prognostic Index.

†See Table 3 for definitions.

‡See Table 1 for definitions. Levels 2-1 through 2-3 were condensed as Level 2 due to the heterogeneity of study designs represented by the references listed and for simplicity.

§The references listed represent the highest level of evidence used to make the treatment recommendation and are not inclusive of all evidence described in the review.

ual disease. Good-risk patients are randomized to receive no further treatment (arm I) or melphalan plus TBI and autologous BMT (arm II). Intermediate- and poor-risk patients receive autologous BMT and are randomized to conditioning with either melphalan alone (arm III), melphalan plus TBI (arm IV), or BEAM (arm V). This study may provide data for comparing the efficacy of 3 preparative regimens for autologous BMT in intermediate/poor–risk lymphomas, and the value of BMT in good-risk patients.

The British National Lymphoma Investigation (BNLI) is conducting a phase III randomized study of early intensification with autologous BMT or PBSCT versus continued standard chemotherapy. Eligible patients must have follicular large cell, diffuse mixed cell, diffuse large cell, or diffuse immunoblastic lymphoma and 2 to 3 Aa-IPI factors. All patients are treated with CHOP × 6 and then randomized to receive BEAM autologous BMT or PBSCT (arm I) or to continue with conventional chemotherapy (arm II).

A Southwest Oncology Group (SWOG) randomized multicenter trial (SWOG-9704) will compare CHOP × 6 and autologous PBSCT in responders with CHOP × 8 cycles followed by autologous PBSCT only at relapse. Patients with intermediate- or high-grade NHL and high-intermediate/high–risk Aa-IPI are eligible for the trial. This study seeks to provide evidence of the utility of PBSCT versus CHOP as primary therapy in poor-risk patients.

The Swiss Institute of Applied Cancer Research is conducting a randomized multicenter trial comparing sequential high-dose chemotherapy with autologous PBSCT with a regimen of CHOP × 6-8 in patients with newly diagnosed diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, and anaplastic large cell lymphoma with at least 1 Aa-IPI factor. Patients in the high-dose sequential therapy arm receive the following 5 regimens:

- Regimen A: doxorubicin, vincristine and prednisone × 1 cycle.
- Regimen B: 3 weeks after regimen A, high-dose cyclophosphamide, G-CSF, and PBSC collections if no BM involvement at diagnosis (if BM involvement at diagnosis, PBSCs are not collected at this time).
- Regimen C: 2 to 3 weeks after regimen B, vincristine and high dose methotrexate.
- Regimen D: 1 to 2 weeks later, methylprednisone and high-dose etoposide; patients with no BM involvement at diagnosis receive G-CSF until count recovery, patients with initial BM involvement receive G-CSF and undergo PBSC collection.
- Regimen E: autologous PBSCT with mitoxantrone and melphalan; patients with bulky disease at diagnosis or residual disease after chemotherapy receive radiation therapy 30 to 100 days after PBSCT.

An NCI-sponsored randomized trial (NCI-V96-1010) is comparing the efficacy and cost-benefit of early intensification including autotransplantation with BEAM versus conventional-dose alternating triple chemotherapy in untreated, intermediate-grade or immunoblastic NHL patients at high risk for relapse. Eligibility requires 3 or more of the following: Ann Arbor stage III/IV disease, B symptoms, tumor mass(es) greater than 7 cm or mediastinal mass visible on chest x-ray, β-2 microglobulin at least 3.0, and LDH level greater than 1.1 times normal. Patients in arm I receive induction with 1 course of idarubicin, cisplatin, cytarabine, and methylprednisone (IDSHAP) and 1 course of methotrexate, leucovorin calcium, idarubicin, vincristine, bleomycin, cyclophosphamide, and methylprednisolone (MBIDCOS). Patients with stable or responding disease receive 3 additional courses every 21 days consisting of 1 course of ifosfamide/etoposide/mesna/G-CSF (2 courses if there are circulating lymphoma cells) and PBSC collection, 1 course of ifosfamide/mitoxantrone/mesna/G-CSF and 1 course of BEAM conditioning for PBSC reinfusion. PBSCs are purged ex vivo prior to reinfusion in patients with a history of BM or PB involvement. Patients in arm II also receive induction with IDSHAP and MBIDCOS, followed by 7 additional courses consisting of alternating courses of MINE (mesna, ifosfamide, mitoxantrone, etoposide), IDSHAP, and MBIDCOS. Each course is given upon hematologic recovery from the previous course.

Posttransplantation Therapy

The Groupe d'Etude des Lymphomes de l'Adulte (GELA) trial is a phase III randomized trial to determine the efficacy of interferon α-2b in reducing the relapse rate in patients treated with PBSCT for recurrent or refractory HD or NHL in second remission [84]. Eligible patients include those with follicular, diffuse small cell, mantle cell, peripheral T-cell, diffuse large B-cell, lymphoblastic, or Burkitt's lymphoma in second CR after autologous SCT, given either as first-line therapy or salvage therapy after first relapse. Patients are stratified by lymphoma subtype and randomized after PBSCT to receive either no further therapy (arm I), or interferon α-2b 3 times weekly for 18 months starting 4 weeks after SCT (arm II). This study may provide evidence of the efficacy of immunotherapy after SCT to prevent relapse.

A SWOG randomized multicenter trial (SWOG 9438) will compare the OS and DFS of patients who receive interleukin (IL)-2 after autologous PBSCT with VCT, with patients who are randomized to observation and no other therapy post-BMT.

C. Unanswered Questions

Whether to have patients undergo transplantation in first CR or to withhold transplantation until patients have demonstrated a chemotherapy-sensitive relapse after first CR is an important unanswered question in DLCL treatment, and one which has been examined only in a nonrandomized prospective trial [85]. Thirty-one patients with diffuse histiocytic lymphoma (30 large cell, 1 mixed cell) and bulky disease and/or elevated serum LDH level were given induction therapy with the L-17M regimen. In the original protocol design, patients were randomized to receive autologous BMT in first CR/PR or to have BMT withheld until relapse. Patients, however, were reluctant to undergo randomization and instead preferred to choose a study arm. As a result, the protocol was revised and patients were allowed to choose up-front BMT versus BMT at relapse.

At a median follow-up of 49+ months, 14 patients who elected to receive autologous BMT in first CR/PR had a

4-year OS of 79% compared with a 4-year OS of 24% in 17 patients who elected to undergo autologous BMT at relapse. There was a significant DFS advantage (P = .002) for the patients who underwent transplantation in first remission (79% survived a median of 49+ months) compared with those who underwent transplantation at relapse (23% survived a median of 5 months). This study was nonrandomized with a small sample size, so no definite conclusions can be reached. A large randomized trial is needed to address the question of transplantation in first remission or first chemotherapy-sensitive relapse.

D. Areas of Needed Research

The following research questions have been identified by this evidence-based review and are grouped into 2 categories: disease-related and treatment-related. Studies to provide clarification of these topics are ongoing or warranted. No priority was assigned, because the topics listed can be studied concurrently.

Disease-Related Research Questions

Should patients be offered SCT in first CR or wait until first chemotherapy-sensitive relapse? The results of ongoing studies are pending.

Should patients receive salvage therapy in first relapse to test for chemotherapy sensitivity, or proceed to SCT in untested relapse?

What is the optimal timing of SC mobilization? Should high-risk patients be mobilized early (ie, in CR1 versus CR2)?

What is the role of post-SCT therapy (chemotherapy; immunotherapy, ie, monoclonal antibodies and vaccination; and radiation therapy)? Which type of post-SCT therapy offers the best improvement in EFS and DFS? Results of ongoing studies are pending.

With greater understanding of the complexity of molecular prognostic factors using gene microarray technology, how will risk-adapted therapy involving SCT be defined?

Treatment-Related Research Questions

What is the role of in vivo versus ex vivo purging using chemical or antibody selection?

Will allogeneic SCTs with nonmyeloablative conditioning regimens offer a graft-versus-lymphoma effect without the toxicity of a myeloablative allogeneic SCT?

What is the role of gene therapy as a part of the conditioning regimen (eg, manipulation of both autologous and allogeneic cells, exogenous or knockout genes) for SCTs?

What is the role of ex vivo expansion in autologous and allogeneic SCTs?

What is the optimal timing of infusion?

Is there a role for dendritic cell therapy?

What are the optimal combinations of chemotherapeutic and immunologic agents, radiation therapy, and gene therapy targets as conditioning regimens to produce the least toxicity and greatest therapeutic effect?

XII. LIMITATIONS OF THIS EVIDENCE-BASED LITERATURE REVIEW

There are limitations to any evidence-based review of the published medical literature. The criteria for this review included reliance on only published data, specifically peer-reviewed articles published since 1980, and abstracts from the 3 most recent years of annual meetings where studies of SCT and/or NHL are presented. Unpublished data, which were not included in this review, often represent "negative" findings and usually do not undergo peer review. We included studies presented in abstract form for the purpose of identifying "negative" clinical trials and preliminary analyses of "positive" clinical trials, with the understanding and acknowledgment that abstracts do not undergo rigorous peer review and do not contain the same level of study detail presented in published articles.

Another limitation of this review is its reliance on published data rather than on individual patient data. The stated goal of the review was to present evidence for making recommendations regarding the role of SCT in the treatment of DLCL. Time and financial constraints made it impractical to obtain data on individual patients from the large number of clinical trials included in this review. Although it was not the objective of this review to perform an extensive meta-analysis of the data, such an analysis is warranted to further clarify the results of studies and address unanswered questions.

Many studies were excluded from this analysis because they did not meet the stringent inclusion criteria for this review, namely the identification of histologic subtypes and the inclusion of at least 70% of patients having DLCL subtype. There were more than 170 publications (100+ abstracts and 70+ manuscripts) that described patients as having "aggressive lymphomas," "intermediate- and high-grade lymphomas," "high-grade lymphomas," and/or "malignant lymphomas" and did not specify the histologic subtypes. More than 80 publications (30+ abstracts and 50+ manuscripts) reported the histologic subtypes, but did not include a sufficient number of DLCL patients to enable the reviewers to reach a conclusion regarding the efficacy of transplantation in this patient population. Most of the publications stated in the abstract or title that the authors studied "aggressive" or "intermediate/high-grade" lymphomas, but there were significant differences in the proportion and distribution of the histologies studied.

Most of the excluded studies addressed transplantation technologies (eg, autologous versus allogeneic donors, PBSCT versus BMT, purged versus unpurged BMT), rather than comparisons between SCT and standard chemotherapy. These included several randomized trials and registry reports comparing autologous and allogeneic BMT for lymphoma patients [86,87] and PBSCT versus BMT in NHL patients [88-93]. These and other studies could have provided much needed evidence in these areas but they could not be included because it was not stated whether the evidence was applicable to DLCL patients.

It should also be noted that inclusion criteria were not based on the availability of patient IPI scores because most of the phase III trials were already accruing patients or had been analyzed prior to publication of the IPI project. It is acknowledged that significant differences in prognosis and outcomes by IPI have been identified, and applicability of results may be problematic if the IPI risk categories of patients are not stated.

XIII. FUTURE INITIATIVES

This comprehensive, systematic review of the available evidence for the role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of diffuse large cell non-Hodgkin's lymphoma is the first in a series of sequential papers sponsored by the American Society for Blood and Marrow Transplantation. Each review will summarize the evidence regarding the role of cytotoxic therapy with SCT in the treatment of a specific disease using defined methodology and grading criteria.

XIV. ACKNOWLEDGMENTS

The ASBMT and Drs. Hahn and McCarthy are indebted to the members of the DLCL Expert Panel and the Steering Committee who voluntarily and enthusiastically participated in this endeavor. The authors acknowledge Dr. C.F. LeMaistre for pioneering and supporting this effort, Mr. Alan Leahigh and Ms. Dianne O'Rourke for their invaluable administrative assistance, and Drs. K.M. Cummings and C. Mettlin for reviewing the manuscript; Allison Miller, Dorothy Macchio and Dr. Marina C. George for serving as replication coders and abstracters; and Dr. Margaret A. Shipp for her research, which was an invaluable foundation for this project, and for her participation in the design and methodology of this review.

APPENDIX A. GLOSSARY OF ABBREVIATIONS

Aa-IPI	Age-adjusted International Prognostic Index (See Appendix B for risk group definitions)
ACVB	Doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisolone
ALCL	Anaplastic large cell lymphoma
ASBMT	American Society for Blood and Marrow Transplantation
BEAC	Carmustine, etoposide, cytarabine, and cyclophosphamide
BEAM	Carmustine, etoposide, cytarabine, and melphalan
BM	Bone marrow
BMT	Bone marrow transplant(ation)
BNLI	British National Lymphoma Investigation
CBV	Cyclophosphamide, carmustine, and etoposide
CEEP	Cyclophosphamide, epirubicin, vindesine, and prednisone
CEOP	Cyclophosphamide, epirubicin, vincristine, and prednisone
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CNS	Central nervous system
CR	Complete response/remission
CRu	CR with scan abnormalities of unknown significance
CT	Cyclophosphamide and TBI
DFS	Disease-free survival
DHAP	Dexamethasone, cisplatin, and cytarabine
DLCL	Diffuse large cell B-cell non-Hodgkin's lymphoma
ECOG	Eastern Cooperative Oncology Group
ECVBP	Epirubicin, cyclophosphamide, vindesine, bleomycin, and prednisone
EFS	Event-free survival
ESHAP	Etoposide, methylprednisolone, high-dose cytarabine, and cisplatin
FFP	Freedom from progression
FFS	Failure-free survival
G-CSF	Granulocyte colony–stimulating factor
GELA	Groupe d'Etude des Lymphomes de l'Adulte
GM-CSF	Granulocyte macrophage–colony stimulating factor
GVHD	Graft-versus-host disease
HD	Hodgkin's disease
HDS	High-dose sequential (therapy)
ICE	Ifosfamide, carboplatin, etoposide
IDSHAP	Idarubicin, cisplatin, cytarabine, and methylprednisone
IF	Induction failure
IFRT	Involved field radiotherapy
IPR	PR to induction therapy
IPI	International Prognostic Index (See Appendix B for risk group definitions)
IWF	International Working Formulation
IWF F	Diffuse mixed small and large cell NHL
IWF G	Diffuse large cell NHL
IWF H	Diffuse large cell immunoblastic NHL
KPS	Karnofsky Performance Status
LDH	Lactate dehydrogenase
LY	Life years
MACOP-B	Methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin
MAD	Mitoxantrone, cytarabine, and dexamethasone
MBIDCOS	Methotrexate, leucovorin calcium, idarubicin, vincristine, bleomycin, cyclophosphamide, and methylprednisolone
MegaCEOP	Cyclophosphamide (1200 mg/m^2), epirubicin (110 mg/m^2), vincristine (1.4 mg/m^2), and prednisone (40 mg/m^2)
MINE	Mesna, ifosfamide, mitoxantrone, etoposide
NCI	National Cancer Institute (U.S.)
NHL	Non-Hodgkin's lymphoma
NS	Not statistically significant
OS	Overall survival
PBSC	Peripheral blood stem cell(s)
PBSCT	Peripheral blood stem cell transplant(ation)
PFS	Progression-free survival
PR	Partial response/remission
ProMACE-MOPP	Prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, mechlorethamine, vincristine, and procarbazine
PS	Performance status
QALY	Quality adjusted life years
REAL	Revised European-American Classification of Lymphoid Neoplasms
RFS	Relapse-free survival
RR	Relative risk
SCT	Hematopoietic stem cell transplant(ation)
SWOG	Southwest Oncology Group

TBI	Total body irradiation
VACOP-B	Etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin
VAPEC-B	Vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, and bleomycin
VCT	Etoposide, cyclophosphamide, and TBI
WHO	World Health Organization

APPENDIX B. DEFINITION OF INTERNATIONAL PROGNOSTIC INDEX MODELS [12]

International Prognostic Index (IPI) Model for All Patients

Risk factors:

Age >60
LDH > normal
ECOG PS > 2
Ann Arbor stage III-IV
>1 extranodal site

Risk Group:	Number of Risk Factors
Low	0-1
Low-intermediate	2
High-intermediate	3
High	4-5

Age-Adjusted International Prognostic Index (AaIPI) Model for Patients ≤60 Years Old

Risk Factors*

LDH > normal
ECOG PS ≥ 2
Ann Arbor stage III-IV

Risk Group	Number of Risk Factors
Low	0
Low-intermediate	1
High-intermediate	2
High	3

*>1 extranodal site of disease was not a significant independent predictor of survival in patients ≤60 years old.

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